



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 January 2013
EMA/163479/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Actelsar HCT

**International non-proprietary name: TELMISARTAN /
HYDROCHLOROTHIAZIDE**

Procedure No. EMEA/H/C/002676/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.



Product information

Marketing authorisation application

| | |
|---|---|
| Name of the medicinal product: | Actelsar HCT |
| Applicant: | Actavis Group hf Reykjavíkurvegur 76-78 220 Hafnarfjörður ICELAND |
| Active substance: | telmisartan / hydrochlorothiazide |
| International Nonproprietary Name/Common Name: | telmisartan / hydrochlorothiazide |
| Pharmaco-therapeutic group (ATC Code): | Angiotensin II receptor antagonists and diuretics (C09DA07) |
| Therapeutic indications: | Treatment of essential hypertension. Actelsar HCT fixed dose combination (40 mg telmisartan/12.5 mg hydrochlorothiazide) is indicated in adults whose blood pressure is not adequately controlled on telmisartan alone. Actelsar HCT fixed dose combination (80 mg telmisartan/12.5 mg hydrochlorothiazide) is indicated in adults whose blood pressure is not adequately controlled on telmisartan alone. Actelsar HCT fixed dose combination (80 mg telmisartan/25 mg hydrochlorothiazide) is indicated in adults whose blood pressure is not adequately controlled on Actelsar HCT 80 mg/12.5 mg (80 mg telmisartan/12.5 mg hydrochlorothiazide) or adults who have been previously stabilised on telmisartan and hydrochlorothiazide given separately. |
| Pharmaceutical form: | tablets |
| Strengths: | 40mg/12.5 mg; 80mg/12.5 mg; 80mg/25 mg |
| | |

| | |
|---------------------------------|--|
| Route of administration: | Oral use |
| Packaging: | blister (Alu/Alu), blister (PVDC/Alu) and bottle (HDPE) |
| Package sizes: | 14 tablets, 28 tablets, 56 tablets, 84 tablets, 90 tablets, 98 tablets, 30 tablets and 250 tablets |

REFERENCE MEDICINAL PRODUCT (USED IN BIOEQUIVALENCE STUDY)

| | |
|---|--|
| Name of the medicinal product: | MicardisPlus |
| Marketing Authorisation Holder | Boehringer Ingelheim International GmbH |
| Active substances: | telmisartan / hydrochlorothiazide |
| International Nonproprietary Name: | telmisartan / hydrochlorothiazide |
| Therapeutic indications: | <p>Treatment of essential hypertension.</p> <p>MicardisPlus fixed dose combination (40 mg telmisartan/12.5 mg hydrochlorothiazide) is indicated in adults whose blood pressure is not adequately controlled on telmisartan alone.</p> <p>MicardisPlus fixed dose combination (80 mg telmisartan/12.5 mg hydrochlorothiazide) is indicated in adults whose blood pressure is not adequately controlled on telmisartan alone.</p> <p>MicardisPlus fixed dose combination (80 mg telmisartan/25 mg hydrochlorothiazide) is indicated in adults whose blood pressure is not adequately controlled on MicardisPlus 80 mg/12.5 mg (80 mg telmisartan/12.5 mg hydrochlorothiazide) or adults who have been previously stabilised on telmisartan and hydrochlorothiazide given separately.</p> |
| Pharmaceutical form: | tablets |
| Strengths: | 40mg/12.5 mg; 80mg/12.5 mg; 80mg/25 mg |
| Route of administration: | Oral use |

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List of abbreviations

| | |
|----------|---|
| HCTZ | Hydrochlorothiazide |
| CEP | Certificate of Suitability of the European Pharmacopoeia |
| XRD | X Ray diffraction |
| HPLC | High Performance Liquid Chromatography |
| HPLC DAD | High-Performance Liquid Chromatography with Diode-Array Detection |
| UV | Ultraviolet spectroscopy |

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Actavis Group hf submitted on 3 May 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Actelsar HCT, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004 – ‘Generic of a Centrally authorised product’. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 15 December 2011.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Treatment of essential hypertension.

Actelsar HCT fixed dose combination (40 mg telmisartan/12.5 mg hydrochlorothiazide) is indicated in adults whose blood pressure is not adequately controlled on telmisartan alone.

Actelsar HCT fixed dose combination (80 mg telmisartan/12.5 mg hydrochlorothiazide) is indicated in adults whose blood pressure is not adequately controlled on telmisartan alone.

Actelsar HCT fixed dose combination (80 mg telmisartan/25 mg hydrochlorothiazide) is indicated in adults whose blood pressure is not adequately controlled on Actelsar HCT 80 mg/12.5 mg (80 mg telmisartan/12.5 mg hydrochlorothiazide) or adults who have been previously stabilised on telmisartan and hydrochlorothiazide given separately.

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and bioequivalence studies with the reference medicinal product MicardisPlus.

Information on paediatric requirements

Not applicable

The chosen reference product is:

■ Medicinal product which is or has been authorised in accordance with Community provisions in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: MicardisPlus 40 mg/12,5 mg, 80 mg/12,5 mg & 80 mg/25 mg tablets
- Marketing authorisation holder: Boehringer Ingelheim Pharma GmbH, Germany
- Date of authorisation: 19-04-2002
- Marketing authorisation granted by:
 - Community
 - Community Marketing authorisation numbers: EU/1/02/213/001-023

■ Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: MicardisPlus 40 mg/12,5 mg, 80 mg/12,5 mg & 80 mg/25 mg tablets
- Marketing authorisation holder: Boehringer Ingelheim Pharma GmbH, Germany
- Date of authorisation: 19-04-2002
- Marketing authorisation granted by:
 - Community
- Community Marketing authorisation numbers: EU/1/02/213/001-023

■ Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: MicardisPlus 80 mg/25 mg tablets
- Marketing authorisation holder: Boehringer Ingelheim Pharma GmbH, Germany
- Date of authorisation: 19-04-2002
- Marketing authorisation granted by:
 - Community
 - Community Marketing authorisation numbers: EU/1/02/213/017-023
- Bioavailability study number(s): 2335-11

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP and the evaluation team were:

Rapporteur: Alar Irs

- The application was received by the EMA on 3 May 2012.
- The procedure started on 23 May 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 August 2012.
- During the meeting on 20 September 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 20 September 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 11 October 2012.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 23 November 2012.
- During the meeting on 10-13 December 2012, the CHMP agreed on the consolidated List of Outstanding Issues to be sent to the applicant. The final consolidated List of Outstanding Issues was sent to the applicant on 14 December 2012.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on

17 December 2012.

- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 27 December 2012.
- During the meeting on 14-17 January 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Actelsar HCT on 17 January 2013.

2. Scientific discussion

2.1. Introduction

Actelsar HCT 40 mg/12.5 mg, 80 mg/12.5 mg and 80 mg/25 mg tablets is a generic medicinal product of MicardisPlus, which has been authorised in the EU since 19 April 2002.

Actelsar HCT is a fixed-dose combination of the active substances telmisartan, a non-peptide angiotensin II receptor (type AT₁) antagonist, and hydrochlorothiazide, a thiazides diuretic. Telmisartan acts as vasodilator and reduces peripheral resistance. It is given in the management of hypertension, heart failure, myocardial infarction and nephropathy. Thiazides such as hydrochlorothiazide (HCTZ) are used in the treatment of hypertension and heart failure.

Telmisartan /hydrochlorothiazide tablets are administered orally for treatment of hypertension. The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone. The effects of fixed dose combination of telmisartan/HCTZ on mortality and cardiovascular morbidity are currently unknown.

The safety and efficacy profile of telmisartan and hydrochlorothiazide has been demonstrated in several clinical trials details of which can be found in the EPAR of MicardisPlus. In addition, there is a long-term post-marketing experience contributing to the knowledge of the clinical use of this product. Since this application is a generic application referring to the reference medicinal product MicardisPlus, summary of the clinical data of telmisartan and hydrochlorothiazide is available and no new clinical studies regarding pharmacology, pharmacokinetics and efficacy and safety have been conducted.

The approved indication is:

Treatment of essential hypertension.

Actelsar HCT fixed dose combination (40 mg telmisartan/12.5 mg hydrochlorothiazide) is indicated in adults whose blood pressure is not adequately controlled on telmisartan alone.

Actelsar HCT fixed dose combination (80 mg telmisartan/12.5 mg hydrochlorothiazide) is indicated in adults whose blood pressure is not adequately controlled on telmisartan alone.

Actelsar HCT fixed dose combination (80 mg telmisartan/25 mg hydrochlorothiazide) is indicated in adults whose blood pressure is not adequately controlled on Actelsar HCT 80 mg/12.5 mg (80 mg telmisartan/12.5 mg hydrochlorothiazide) or adults who have been previously stabilised on telmisartan and hydrochlorothiazide given separately.

The indication proposed for Actelsar HCT is the same as authorized for the Reference medicinal product.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as tablets containing 40 mg/12.5 mg, 80 mg/12.5 mg and 80 mg/25 mg of telmisartan and hydrochlorothiazide as active substances. The composition is described in section 6.1 of the SmPC.

Actelsar HCT 40 mg/12.5 mg are 6.55 x 13.6 mm oval, biconvex tablets marked with "TH" on one side. Actelsar HCT 80/12.5 mg are 9 x 17 mm capsule shape tablets, white or almost white, marked with "TH 12.5" on both sides. Actelsar HCT 80 mg/25 mg are 9.0 x 17.0 mm oval, biconvex tablets marked with "TH" on one side and "25" on the other side.

The product is available in blisters as described in section 6.5 of the SmPC.

2.2.2. Active substance

Telmisartan

Telmisartan is a white to off-white crystalline powder, slightly hygroscopic, practically insoluble in water, slightly soluble in methanol, sparingly soluble in methylene chloride and freely soluble in organic solvents. The chemical name is:

4'-[[4-Methyl-6-(1-methyl-1H-benzimidazol-2-yl)-2-propyl-1Hbenzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid.

Telmisartan has no chiral centres and exhibits no stereoisomerism. The active substance exhibits polymorphism. Differential scanning calorimetry studies confirm that the manufacturing process used consistently produces the same polymorphic form.

As there is a monograph of telmisartan in the European Pharmacopoeia, the manufacturer of the active substance, has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for telmisartan which has been provided within the current Marketing Authorisation Application.

Manufacture

A Certificate of Suitability (CEP) has been granted for the active substance. The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

Specification

The active substance will be tested and assessed by the finished product manufacturer applying the methods and specifications laid down in the Ph. Eur. monograph and CEP of telmisartan.

Stability

The CEP of the active substance manufacturer includes a suitably validated re-test period in a defined container closure system, supported by the available stability data.

Hydrochlorothiazide

Hydrochlorothiazide (HCT) is a white or almost white crystalline powder, very slightly soluble in water, soluble in acetone, sparingly soluble in ethanol (96 per cent). The chemical name is: 6-Chloro-3, 4-dihydro-2H-1, 2, 4-benzothiadiazine-7-sulfonamide 1, 1-dioxide.

Hydrochlorothiazide does not show optical activity or different potential isomers. It shows polymorphism. The manufacturing process consistently produces the same polymorphic form.

As there is a monograph of hydrochlorothiazide in the European Pharmacopoeia, the manufacturers of the active substance, have been granted Certificates of Suitability of the European Pharmacopoeia (CEP) for hydrochlorothiazide which have been provided within the current Marketing Authorisation Application.

Manufacture

A Certificate of Suitability (CEP) has been granted for the active substance. The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

Specification

The active substance will be tested and assessed by the finished product manufacturer applying the methods and specifications laid down in the Ph. Eur. monograph and CEP of hydrochlorothiazide.

Stability

The CEP includes a suitably validated re-test period in a defined container closure system, supported by the available stability data.

2.2.3. Finished medicinal product

Pharmaceutical development

The aim of the development was to formulate an oral dosage form consisting of a fixed dose combination of telmisartan and hydrochlorothiazide. The tablets were intended to show essential similarity with the reference product Micardisplus 40/12.5 mg, 80/12.5 mg and 80/25 mg tablets.

The excipients used in the formulation were all compendial, well known and widely used for this dosage form. The excipients used include: magnesium stearate (lubricant), potassium hydroxide (pH regulator), meglumine (pH regulator), povidone (binder/crystallization retarder), sodium starch glycolate (disintegrant), microcrystalline cellulose (filler/binder), mannitol (filler), purified water (granulation liquid), and ethanol 96% (granulation liquid).

The reference product is manufactured as a double layer tablet to solve the incompatibility issues between telmisartan and hydrochlorothiazide, whereas Actelsar HCT has been formulated as a mono tablet. The incompatibility between the two active substances has been solved by carefully controlling the pH during the manufacturing process to ensure that hydrochlorothiazide is stable and telmisartan does not precipitate.

A bioequivalence study was performed to demonstrate the bioequivalence of Actelsar HCT with the reference product. The highest strength (80/25 mg) was selected for the bioequivalence study. It has

been concluded that the test product, Actelsar HCT 80/25 mg, is bioequivalent to the reference product, MicardisPlus 80/25 mg in healthy adults, under fasting conditions.

The additional strengths of the product series, 40/12.5 mg and 80/12.5 mg, have not been tested *in vivo* for bioequivalence. Exemption of a bioavailability study for the 40/12.5 mg and 80/12.5 mg strengths was acceptable since all requirements of a biowaiver for these strengths have been fulfilled. The formulation used during clinical studies is the same that the used for marketing.

The primary packaging proposed is Al/Al blisters, Al/PVC/PVDC blisters or HDPE containers with LDPE lid. The material complies with PhEur requirements and it is adequate to support the stability and use of the product.

Adventitious agents

No excipients derived from animal or human origin have been used.

Manufacture of the product

The manufacturing process consists of thirteen main steps including blending, sieving, granulation, drying, tableting and packaging. The process is considered to be a standard manufacturing process.

The manufacturing process has been adequately described and the critical steps have been identified. In-process controls are adequate for this tablet preparation and are performed during granulation, tableting and packaging.

The validation protocol proposed for the full scale batches has been provided and the quality of the production batches will be evaluated through the results of in process testing as well as the results of finished product testing.

The batch analysis data on seven pilot scale batches shows that the tablets can be manufactured reproducibly according to the agreed finished product specification, which is suitable for the control of this oral preparation.

Product specification

The finished product release specification includes appropriate tests for: description (visual examination), identification of telmisartan and hydrochlorothiazide (High Pressure Liquid Chromatography-HPLC and HPLC with Diode Array Detector-DAD), uniformity of dosage units (Ph. Eur.), average weight of 10 tablets, disintegration (Ph. Eur.), dissolution (Ultra-violet-UV), assay (HPLC), related substances (HPLC) and microbiological purity (Ph. Eur.).

Batch analysis results on two pilot scale batches for the 40 mg/12.5 mg and 80 mg/25 mg strengths and three pilot scale batches for the 80 mg/12.5 mg strength were in accordance with the proposed specification. The CHMP concluded that the specification limits for dissolution for the higher strengths (80mg/12.5mg; 80mg/25mg) of the finished product can be accepted considering the discriminatory nature of the dissolution test. However, the specification limits should be re-evaluated, when further batch results for commercial size batches are available, in order to tighten the limits.

Stability of the product

Stability data of two pilot scale batches for the 40 mg/12.5 mg and 80 mg/25 mg strengths and three pilot scale batches for the 80 mg/12.5 mg strength stored under long term conditions for 12 months at

25°C/60%RH and for up to six months under accelerated conditions at 40°C/75%RH according to ICH guidelines were provided. The batches of Actelsar HCT are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for description, identification, uniformity of dosage units, average weight of 10 tablets, disintegration, dissolution, assay, related substances, microbiological purity and resistance to crushing. The analytical procedures used were stability indicating.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products.

Based on available stability data, the proposed shelf-life as stated in the SmPC is acceptable.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

The CHMP recommends the re-evaluation of the specification limits for dissolution for the higher strengths (80mg/12.5mg; 80mg/25mg) of the finished product and if appropriate to tighten the specification when further batch results for commercial size batches are available.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Pharmacology

Environmental Risk Assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Actelsar HCT manufactured by Actavis hf. is considered unlikely to result in any significant increase in the combined sales volumes for all telmisartan / hydrochlorothiazide containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for Actelsar HCT tablets containing telmisartan / hydrochlorothiazide. To support the marketing authorisation application the applicant conducted two bioequivalence studies, one pilot study No. 2043/10 and one pivotal study No. 2335/11, with the highest telmisartan / hydrochlorothiazide 80/25 mg strength.

Pivotal study No. 2335/11: A randomized, open label, two treatment, four period, two sequence, single dose, crossover, fully replicate, bioequivalence study of tablets containing Fixed Dose Combination (FDC) of telmisartan 80 mg and hydrochlorothiazide 25 mg of Actavis Group PTC ehf. Iceland and Micardis Plus (telmisartan and hydrochlorothiazide) 80/25 mg tablets of Boehringer Ingelheim Pharma GmbH, Germany, in healthy adult subjects, under fasting conditions.

Pilot bioequivalence study no. 2043/10: A randomized, open label, three treatment, three period, three sequence, single dose, crossover, pilot, bioequivalence study of two test formulations of fixed dose combination (FDC) tablets containing telmisartan 80 mg and hydrochlorothiazide 25 mg of Actavis Group PTC ehf, Iceland and Micardis Plus (telmisartan 80 mg and hydrochlorothiazide 25 mg) tablets of Boehringer Ingelheim International GmbH, Germany, in healthy adult subjects, under fasting conditions.

The applicant claims for a biowaiver for the telmisartan / hydrochlorothiazide 40/12.5 mg and 80/12.5 mg strengths, which was acceptable to the CHMP (see Pharmacokinetics below).

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of telmisartan / hydrochlorothiazide based on published literature. The SmPC is in line with the SmPC of the reference product.

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment 'Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1' in its current version is of particular relevance.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Clinical studies

To support the marketing authorisation application the applicant conducted two bioequivalence studies, one pilot study No. 2043/10 and one pivotal study No. 2335/11, with the highest telmisartan / hydrochlorothiazide 80/25 mg strength.

2.4.2. Pharmacokinetics

According to the SmPC of the reference product MicardisPlus, the pharmacokinetics of telmisartan is non-linear with more than dose proportional increase in C_{max} and AUC. As per literature references submitted by the Applicant, the pharmacokinetics of hydrochlorothiazide is linear over the dose range of 12.5 mg to 25 mg.

According to the SmPC, the reference product can be taken with or without food.

Therefore, choice of strength, the highest telmisartan / hydrochlorothiazide 80/25 mg tablets, and design of the pivotal study, a single dose crossover bioequivalence study under fasting condition, are appropriate and in line with the Guideline on the Investigation of Bioequivalence.

Pivotal study No. 2335/11

Study design

A single dose, replicate design bioequivalence study under fasting conditions to demonstrate essential similarity between the test and reference product was conducted. This was an open label randomised study.

Test and reference products

Test Product:

Name: Telmisartan / hydrochlorothiazide

Dosage form/Route of administration: Tablet / Oral

Regimen: Single dose of 1 x 80 mg/25 mg

Reference Product:

Name: MicardisPlus

Dosage form/Route of administration: Tablet / Oral

Regimen: Single dose of 1 x 80 mg/25 mg

Population(s) studied

48 healthy male subjects enrolled in the study, 43 were included in the pharmacokinetic and statistical analysis. Healthy male subjects (21 to 43 years of age) with a normal weight, liver and kidney function and no prior drug use were admitted.

Analytical methods

LC-MS/MS methods were used for the determination of plasma concentrations of both analytes, for telmisartan solid phase extraction and for HCTZ liquid extraction was used for sample preparation.

The analytical range for telmisartan was 1.990 to 1022.298 ng/ml in the biostudy.

For hydrochlorothiazide the calibration curve ranged from 1.053 ng/ml to 298.438 ng/ml in the biostudy.

Analytical methods were appropriately validated and met the criteria of the Guideline on Bioanalytical Method Validation.

Pharmacokinetic Variables

The pharmacokinetic parameters determined were C_{max}, T_{max}, AUC_t, AUC_∞, AUC_{t/∞}, Kel and T_{1/2el}, which were measured and calculated from the collected blood samples for telmisartan and hydrochlorothiazide. The main PK parameters were estimated using a non-compartmental approach with a log-linear terminal phase assumption. The trapezoidal rule was used to estimate the area under the curve and the terminal phase was estimated by maximizing the coefficient of determination estimated from the log-linear regression model. The natural logarithmic transformation of C_{max}, AUC_t and AUC_∞ as well as the rank-transformation of T_{max} were used for all statistical analysis.

Statistical methods

The statistical analysis was carried out according to the bioequivalence guideline. This means natural log transformation of the data and analysis of variance. A linear mixed effects model (Proc Mixed of SAS) for repeated measurements included as main factors periods, sequences and formulations as fixed effects. Subjects were considered as a random factor. AUC_{0-t} and C_{max} were the primary pharmacokinetic variables in this study. The bioequivalence criteria were based on the 90%CI of the ratio (test product/reference product) of least square means from the ANOVA of the log-transformed AUC_{0-t} and C_{max}. The resulting interval had to fit within the equivalence interval of 80.00% to 125.00% for telmisartan AUC and hydrochlorothiazide AUC / C_{max}.

A claim of bioequivalence was based on the AUC_{0-t} and C_{max}.

Software SAS package 9.2 was used for statistical analysis.

Standard statistical analysis using ANOVA and linear mixed effects model were used and are considered acceptable methods. Widening of the 90%CI of C_{max} of telmisartan had been pre-specified, and is acceptable for a replicate design study.

In addition, a pilot bioequivalence study was conducted in 27 healthy volunteers; the study had non-replicate design (see discussion below). Bioequivalence was demonstrated for AUC_t and C_{max} both for telmisartan and for hydrochlorothiazide. Hence, the choice of replicate design and pre-specified widening of 90%CI of C_{max} of telmisartan were not supported by the results from the pilot study.

Results

A total of 43 subjects were analysed.

Summary of pharmacokinetic parameters for the test and reference product is presented in Table 3.1.A.

Table 3.1.A Pharmacokinetic data for Telmisartan in 2335/11

| Pharmacokinetic parameter | Arithmetic Means (±SD) | |
|-------------------------------|------------------------|--------------------------------|
| | Test Product | Reference Product ¹ |
| AUC _(0-t) | 3153.02 (±) 2149.007 | 3062.55 (±) 1890.097 |
| AUC _(0-∞) | 3390.65 (±) 2264.971 | 3235.93 (±) 1996.743 |
| C _{max} | 397.33 (±) 274.194 | 409.33 (±) 230.885 |
| T _{max} ² | 1.33 (0.67, 4.00) | 1.00 (0.33, 3.00) |

Summary of pharmacokinetic parameters for the test and reference product is presented in Table 3.1.B.

Table 3.1.B Pharmacokinetic data for Hydrochlorothiazide in 2335/11

| Pharmacokinetic parameter | Arithmetic Means (\pm SD) | |
|--|------------------------------|--------------------------------|
| | Test Product | Reference Product ¹ |
| AUC _(0-t) | 1172.15 (\pm) 243.049 | 1275.78 (\pm) 343.768 |
| AUC _(0-∞) | 1203.99 (\pm) 247.885 | 1307.55 (\pm) 351.180 |
| C _{max} | 144.78 (\pm) 33.395 | 165.21 (\pm) 49.773 |
| T _{max} ² | 2.00 (0.67 , 4.00) | 1.33 (0.67 , 4.00) |

¹ Pooled Arithmetic Means (\pm SD) is provided for Reference Product

² Median (Min, Max)

Statistical analysis

Results for telmisartan are presented in Table 3.3.A.

Table 3.3.A Bioequivalence evaluation of Telmisartan in 2335/11

| Pharmacokinetic parameter | Ratio Test / Ref | Confidence Intervals | CV% ¹ |
|--|------------------|----------------------|------------------|
| AUC _(0-t) | 103.01 % | 98.43 % - 107.80 % | 16.50 % |
| AUC _(0-∞) | 104.73 % | 99.42 % - 110.32 % | 16.97 % |
| C _{max} | 94.62 % | 86.31 % - 103.73% | 32.44 % |

The bioequivalence study had replicate design and intrasubject coefficient of variance was calculated from the two administrations of the reference product:

Intrasubject CV% of C_{max} of telmisartan was 32.44%, hence, the scaled widening of 90%CI of the C_{max} would be acceptable. However, the 90% CI lied within the standard 80.00%-125.00%.Results for hydrochlorothiazide are presented in Table 3.3.B.

Table 3.3.B Bioequivalence evaluation of Hydrochlorothiazide in 2335/11

| Pharmacokinetic parameter | Ratio Test / Ref | Confidence Intervals | CV% ¹ |
|--|------------------|----------------------|------------------|
| AUC _(0-t) | 93.89 % | 88.02 % - 100.15 % | 17.06 % |
| AUC _(0-∞) | 94.07 % | 88.30 % - 100.21 % | 16.83 % |
| C _{max} | 89.91 % | 83.23 % - 97.13 % | 20.20 % |

¹ Estimated from the Residual Mean Squares. For replica design studies report the within-subject CV% using only the reference product data.

Safety data

There were no serious adverse events in the study. There were 60 adverse events reported in the study out of which 56 events were considered related to study products and 4 events were considered to be unrelated to the study products. Among the 56 events, 30 events were assessed to be related to the test product and 26 events to the reference product. All adverse events were mild to moderate in intensity and resolved completely without sequelae. Based on the review of the clinical and laboratory safety data, both the test and reference product were found to be safe and well tolerated.

Conclusions pivotal study

This study shows that the requirements for claiming bioequivalence of the described test-formulation are fulfilled: for all key pharmacokinetic parameters, listed in the relevant guidelines, the 90% CI of the AUC and Cmax ratio's for telmisartan and hydrochlorothiazide are within the classical 80.00% - 125.00% range. The study design and conduct were valid and appropriate, the chemical analysis was sufficiently sensitive and no serious invalidating protocol deviations were noted. The washout period of 12 days was sufficiently long. The pharmacokinetics of telmisartan is nonlinear with more than dose proportional increase in plasma concentration (Cmax and AUC). Hydrochlorothiazide pharmacokinetics are reported to be linear (Dollery C. ed [1999] HCTZ in Therapeutic Drugs Churchill Livingstone, London). It is therefore appropriate to conduct the bioequivalence study on the highest strength and the results of this bioequivalence study can be extrapolated to other dosage strengths.

Pilot bioequivalence study no. 2043/10

A randomized, open label, three treatment, three period, three sequence, single dose, crossover, pilot, bioequivalence study of two test formulations of fixed dose combination (FDC) tablets containing telmisartan 80 mg and hydrochlorothiazide 25 mg of Actavis Group PTC ehf, Iceland and Micardis Plus (telmisartan 80 mg and hydrochlorothiazide 25 mg) tablets of Boehringer Ingelheim International GmbH, Germany, in healthy adult subjects, under fasting conditions".

A total of 27 healthy adult male subjects were enrolled for the study. 22 subjects completed the study. 25 subjects were included in the final statistical analysis of AUC and Cmax. The pilot study was a three period crossover bioequivalence study. Two formulations of the test product were tested.

Bioequivalence between the generic Actavis Group PTC ehf telmisartan/HCTZ 80/25 mg and the reference product MicardisPlus 80/25 mg was demonstrated in this pilot study.

Biowaiver

The applicant claims for a biowaiver for the lower telmisartan / hydrochlorothiazide 40/12.5 mg and 80/12.5 mg strengths.

The extrapolation is valid as the following requirements are fulfilled:

- a) the products are manufactured by the same manufacturing process,
- b) the qualitative composition of the different strengths is the same,
- c) the ratio between amounts of active substance and excipients is the same,
- d) appropriate in vitro dissolution data are present and similar in outcome.

If there are some deviations from quantitative proportionality point c) above is still valid if either i) and ii) or i) and iii) below are fulfilled:

- i) the amount of active substance is less than 5% of the tablet core weight,
- ii) the amounts of different core excipients or capsule content are the same and only the amount of active substance is changed,
- iii) the amount of filler is changed to account for the change in active substance.

The ratios are the same for all ingredients in 40/12.5 mg and 80/25 mg. The only variations in the ratios are in the 80/12.5 mg tablet for HCTZ (below 5%) and for Mannitol (filler). As all the above requirements are fulfilled the bioequivalence results from the study on telmisartan / hydrochlorothiazide 80/25 mg can be used to waive studies on the lower strengths.

Overall Pharmacokinetic Conclusion

Bioequivalence between the generic Actavis Group PTC ehf telmisartan / hydrochlorothiazide 80/25 mg and the reference product MicardisPlus 80/25 mg was demonstrated in the pivotal bioequivalence study. Data submitted to support a biowaiver claim for telmisartan / hydrochlorothiazide 40/12.5 mg tablets and 80/12.5 mg tablets are acceptable.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

This application concerns the generic medicinal product Actavis Group PTC ehf telmisartan / hydrochlorothiazide 40/12.5 mg tablets, 80/12.5 mg tablets and 80/25 mg tablets.

The pivotal study was a single dose replicate design bioequivalence study under fasting conditions conducted to demonstrate essential similarity with the reference product MicardisPlus (Boehringer Ingelheim GmbH, Germany). The reference product MicardisPlus can be taken with or without food, hence, a fasting study is acceptable. Selection of the highest telmisartan / hydrochlorothiazide 80/25 mg strength is appropriate since according to the SmPC of the reference product, telmisartan has non-linear PK with more than dose proportional increase in AUC. As per submitted literature references, PK of hydrochlorothiazide is linear over the dose range of 12.5 mg to 25 mg. The pivotal study had a replicate design. A pilot non-replicate design bioequivalence study was conducted in 27 healthy volunteers. Bioequivalence was demonstrated for AUCT and C_{max} both for telmisartan and for hydrochlorothiazide. Hence, the choice of replicate design and pre-specified widening of 90%CI of C_{max} of telmisartan were not supported by the results from a pilot study. However, overall the design and conductance of the study was acceptable and in line with the Guideline on the Investigation of Bioequivalence.

For the highest telmisartan / hydrochlorothiazide 80/25 mg strength bioequivalence between the generic Actavis Group PTC ehf tablets and the EU reference product MicardisPlus has been demonstrated both for C_{max} (telmisartan 94.62 [90%CI 86.31 ; 103.73]; HCTZ 89.91 [90%CI 83.23 ; 97.13]) and for AUCT (telmisartan 103.01 [90% CI 98.43 ; 107.80]; HCTZ 93.89 [88.02 ; 100.15]).

A biowaiver claim has been submitted for the additional 40/12.5 mg and 80/12.5 mg strengths. All criteria for a biowaiver according to the Guideline on the Investigation of Bioequivalence are fulfilled.

2.4.6. Conclusions on clinical aspects

In conclusion, bioequivalence has been shown between the generic test product Actavis Group PTC ehf telmisartan / hydrochlorothiazide 40/12.5 mg tablets, 80/12.5 mg tablets and 80/25 mg tablets and the reference product MicardisPlus (Boehringer Ingelheim GmbH, Germany).

With reference to the 40/12.5 mg and 80/12.5 mg strengths, all criteria for a biowaiver according to the Guideline on the Investigation of Bioequivalence are fulfilled.

2.5. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

During the procedure, the applicant replaced the detailed description of the pharmacovigilance system (DDPS) with the summary of pharmacovigilance system, which is acceptable.

Risk management plan

The CHMP did not require the applicant to submit a risk management plan since the application concerns a generic with a reference medicinal product for which no safety concerns require additional risk minimisation activities.

The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product.

No additional risk minimisation activities were required beyond those included in the product information.

PSUR submission

At the time of granting the marketing authorisation, the submission of periodic safety update reports is not required for this medicinal product. However, the marketing authorisation holder shall submit periodic safety update reports for this medicinal product if the product is included in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to MicardisPlus 40mg/12.5mg tablets. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of telmisartan / hydrochlorothiazide tablets. The reference product MicardisPlus is indicated for treatment of essential hypertension. No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study 2335/11 forms the pivotal basis with a single dose, randomised, replicate design under fasting conditions. The study design was considered adequate to evaluate the

bioequivalence of this formulation and was in line with the respective European requirements. The reference product MicardisPlus can be taken with or without food; hence, a fasting study is considered acceptable. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Actelsar HCT met the protocol-defined criteria for bioequivalence when compared with the reference product. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range of 80.00 to 125.00%. Bioequivalence of the two formulations was demonstrated.

In addition, with reference to the additional 40/12.5 mg and 80/12.5 mg strengths, all criteria for a biowaiver according to the Guideline on the Investigation of Bioequivalence are fulfilled.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Actelsar HCT in the treatment of essential hypertension is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to prescription.

Conditions and requirements of the Marketing Authorisation

Pharmacovigilance System

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

Risk management system

Not applicable.

PSUR cycle

At the time of granting the marketing authorisation, the submission of periodic safety update reports is not required for this medicinal product. However, the marketing authorisation holder shall submit periodic safety update reports for this medicinal product if the product is included in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.